

U.S. Application Serial No. 09/700,806
Supplement Amendment dated February 1, 2006
Response to Office Action of September 1, 2005

Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1. (currently amended) A method of treating a nitric oxide (NO) associated disorder in a mammal, wherein the disorder is hypertension, thrombosis, angina, atherosclerosis, or heart failure, comprising administering to said mammal an effective amount of VEGF receptor agonist that exhibits selective binding affinity for a KDR receptor and induces NO production in the mammal, wherein the agonist comprises a VEGF variant having:

- a) one or more amino acid substitutions at or between residues F17 to Y25, wherein one or more of M18, Y21, Q22, or Y25 is substituted; and
- b) one or more amino acid substitutions at or between residues D63 to E67; wherein the binding affinity of the agonist for FLT-1 receptor is reduced as compared to the binding affinity of native VEGF for FLT-1 receptor.

2-7. (cancelled)

8. (original) The method of claim 1 wherein said mammal is a human.

9. (cancelled)

10. (previously presented) The method of claim 1 wherein said effective amount of VEGF receptor agonist enhances nitric oxide production in said mammal.

11-22. (cancelled)

23. (currently amended) The method of claim 1, wherein the amino acid substitution(s) of (b) comprises D63S, G63M, or L66R.

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24. (currently amended) The method of claim 23, wherein the amino acid substitutions of (b) comprise D63S, G65M, and L66R.

25-27. (cancelled)

28. (currently amended) The method of claim 27₁, wherein the amino acid substitution(s) of (a) comprises one or more of M18E, Y21L, Q22R, or Y25S.

29. (currently amended) The method of claim 28, wherein the amino acid substitutions of (a) comprise M18E, Y21L, Q22R, and Y25S.

30. (currently amended) The method of claim 27₁, wherein the VEGF variant comprises one of the following combinations of amino acid substitutions:

- (a) M18E, D63S, G65M, and L66R;
- (b) Y21L, D63S, G65M, and L66R;
- (c) Q22R, D63S, G65M, and L66R;
- (d) Y25S, D63S, G65M, and L66R;
- (e) M18E, Y21L, D63S, G65M, and L66R;
- (f) M18E, Q22R, D63S, G65M, and L66R;
- (g) M18E, Y25S, D63S, G65M, and L66R;
- (h) Y21L, Q22R, D63S, G65M, and L66R;
- (i) Y21L, Y25S, D63S, G65M, and L66R;
- (j) Q22R, Y25S, D63S, G65M, and L66R;
- (k) M18E, Y21L, Q22R, D63S, G65M, and L66R;
- (l) M18E, Q22R, Y25S, D63S, G65M, and L66R;
- (m) Y21L, Q22R, Y25S, D63S, G65M, and L66R;
- (n) M18E, Y21L, Q22R, Y25S, and D63S;
- (o) M18E, Y21L, Q22R, Y25S, and G65M;
- (p) M18E, Y21L, Q22R, Y25S, and L66R;
- (q) M18E, Y21L, Q22R, Y25S, D63S, and G65M;

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- (r) M18E, Y21L, Q22R, Y25S, D63S, and L66R;
- (s) M18E, Y21L, Q22R, Y25S, G65M, and L66R; or
- (t) M18E, Y21L, Q22R, Y25S, D63S, G65M, and L66R.

31-38. (cancelled)

39. (previously presented) The method of claim 1, wherein NO production is sustained for more than 24 hours.

40. (previously presented) The method of claim 1, wherein NO production is sustained for at least 2 days.

41. (currently amended) The method of claim 141, wherein NO production is sustained for at least 3 days.

42. (currently amended) The method of claim 141, wherein upregulation of eNOS NO production is sustained for at least 4 days.